National Cancer Institute

Using Genetic Data to Further Understand the Role that Environmental Exposures Play in Bladder Cancer Etiology

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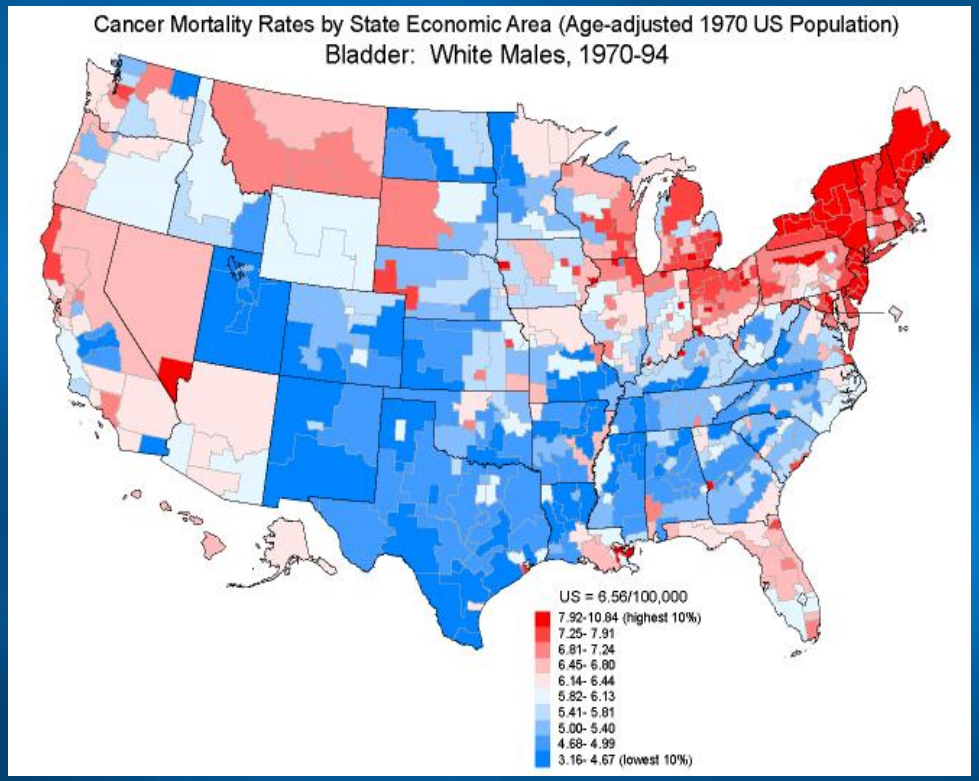
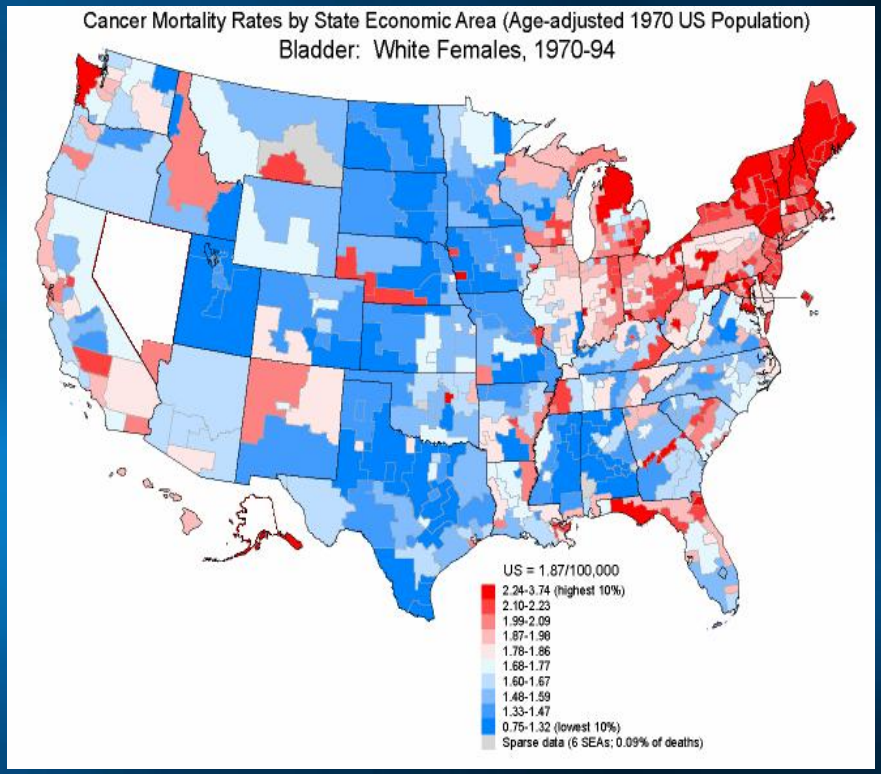
Overwhelming evidence that most bladder cancer is caused by environmental exposures

- Tobacco (aromatic amines, e.g., 4-aminobiphenyl)
- Occupational exposure to aromatic amine dyes (benzidine, beta-naphthylamine)
- Environmental arsenic

Excess Bladder Cancer Mortality in Males and Females in New England



Males, 1970-94



Females, 1970-94

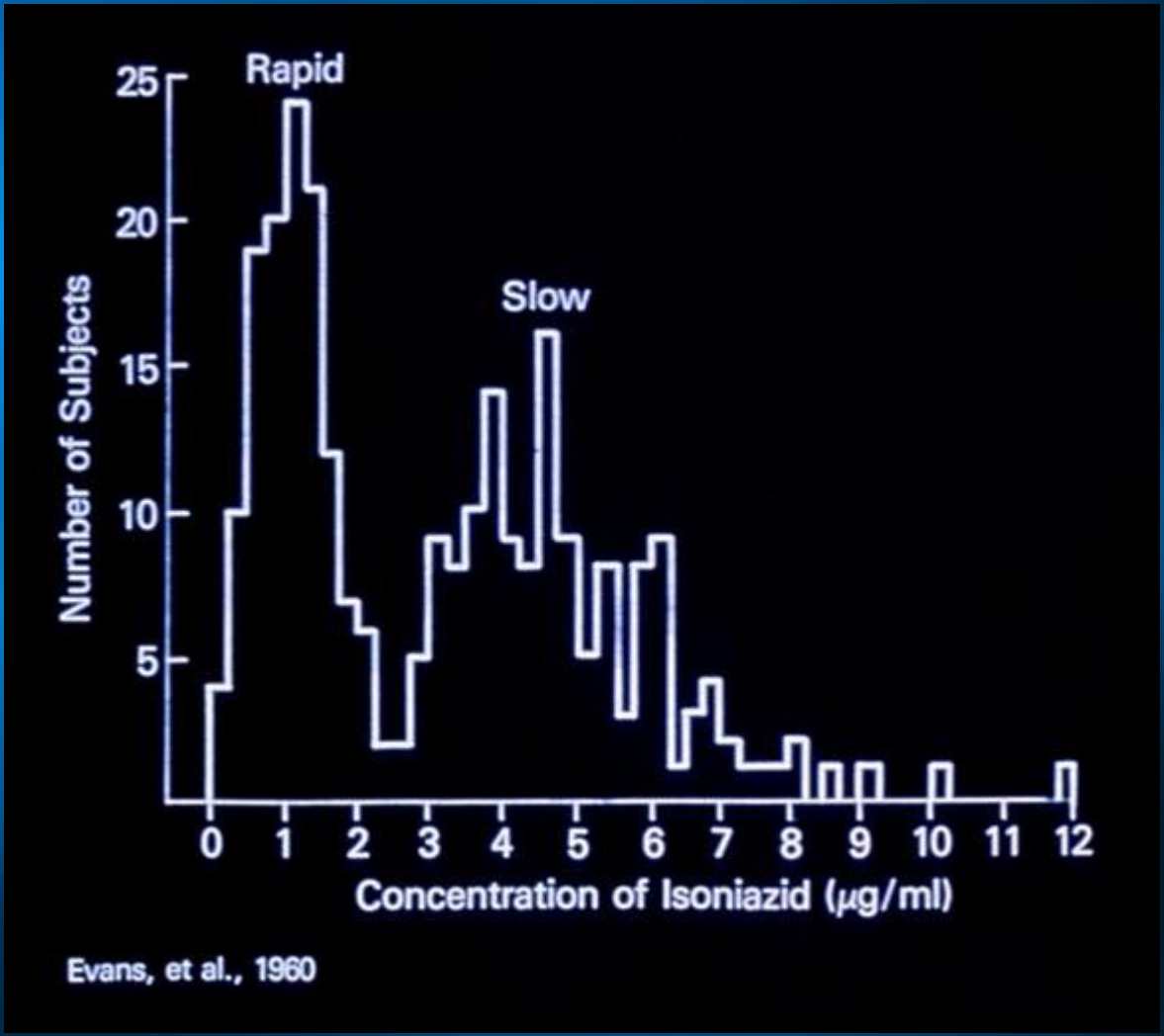
Source: Atlas of Cancer Mortality in the United States, 1950-1994, NCI

Why study genetic modification of the fundamental forces that drive bladder (and most) cancer risk in most populations?

- Obtain mechanistic insight
- More effectively evaluate low levels of risk
- Develop more effective prevention and treatment strategies
- Identify new environmental health hazards

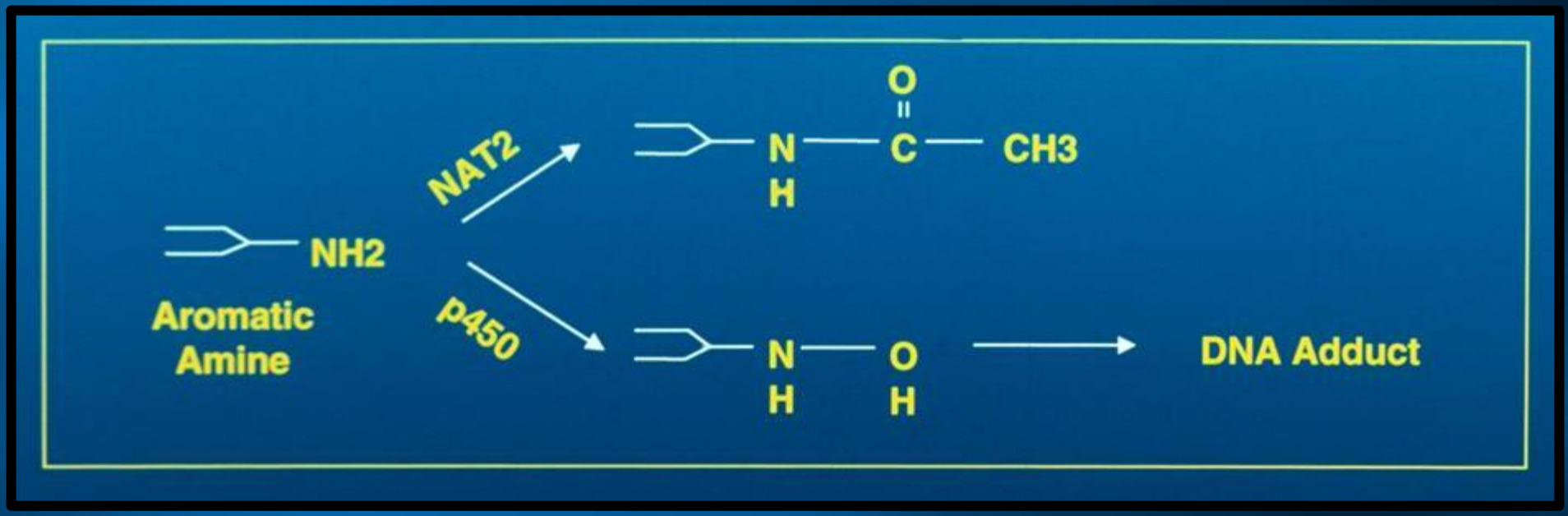
Aromatic Amine Exposure, *NAT2* Slow Acetylation, and Bladder Cancer

N-Acetylation Polymorphism and (*NAT2*) Isoniazid Clearance from Plasma



Detoxification of Aromatic Amines by N-Acetylation

(Lower et al., EHP 1979)



NAT2 Slow Acetylation Genotype and Bladder Cancer Risk

- General population (6360 cases, 41 studies):

  OR =1.35, 95%CI: 1.21-1.50, p = 10^{-6}

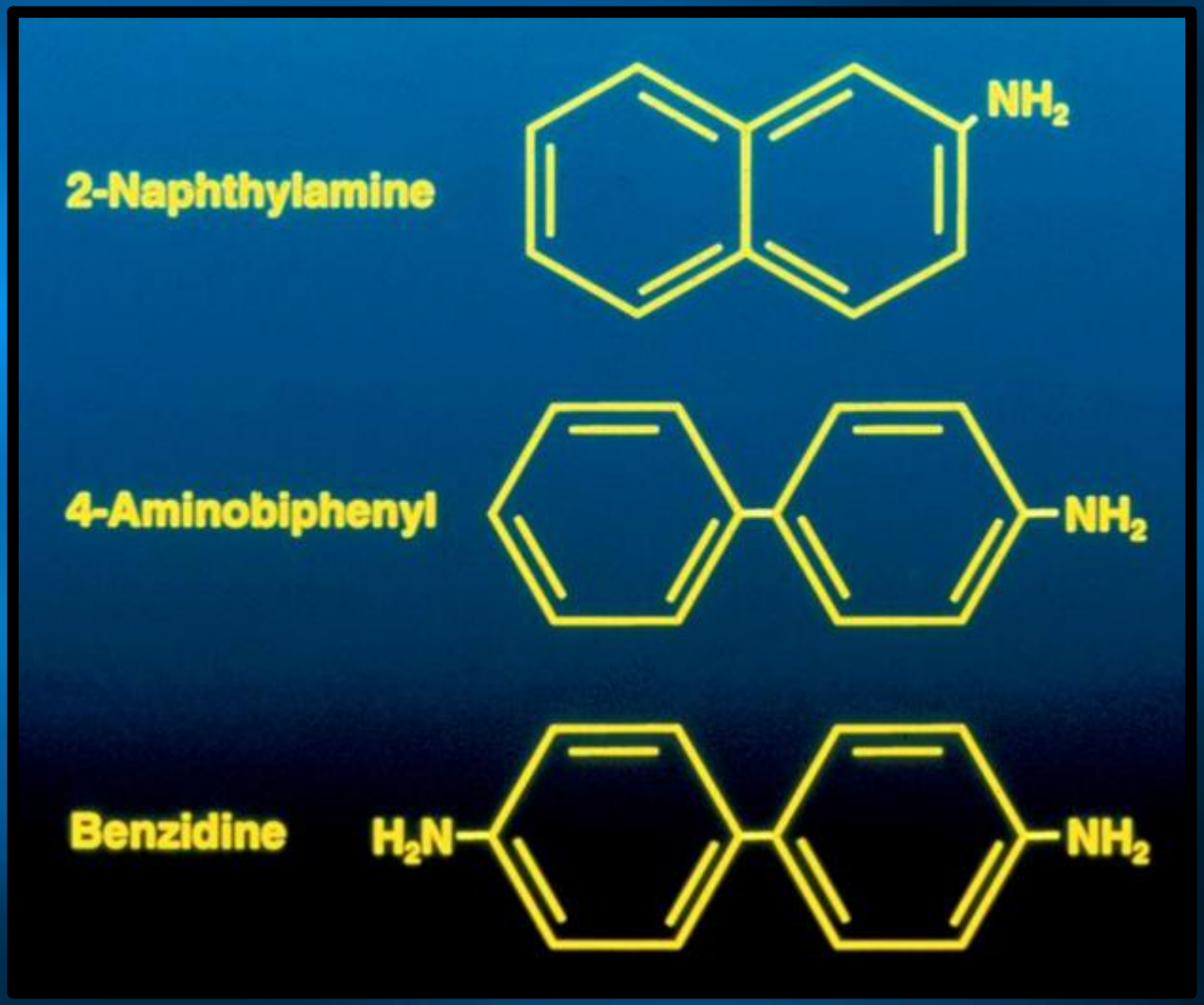
- Case-only interaction OR of effect in Smokers/Non-smokers (4305 cases, 22 studies)

  OR = 1.2, 95%CI: (1.1-1.5) p = 0.008;

  OR = 1.3 for Caucasians only

(Garcia-Closas et al., Lancet 2005; Rothman et al., IJE, 2007, Garcia-Closas in prep)

Carcinogenic Aromatic Amines



NAT2 Slow Acetylation Genotype and Bladder Cancer Risk, By Aromatic Amine exposure

- **Benzidine-exposed workers (68 cases, 2 studies):**

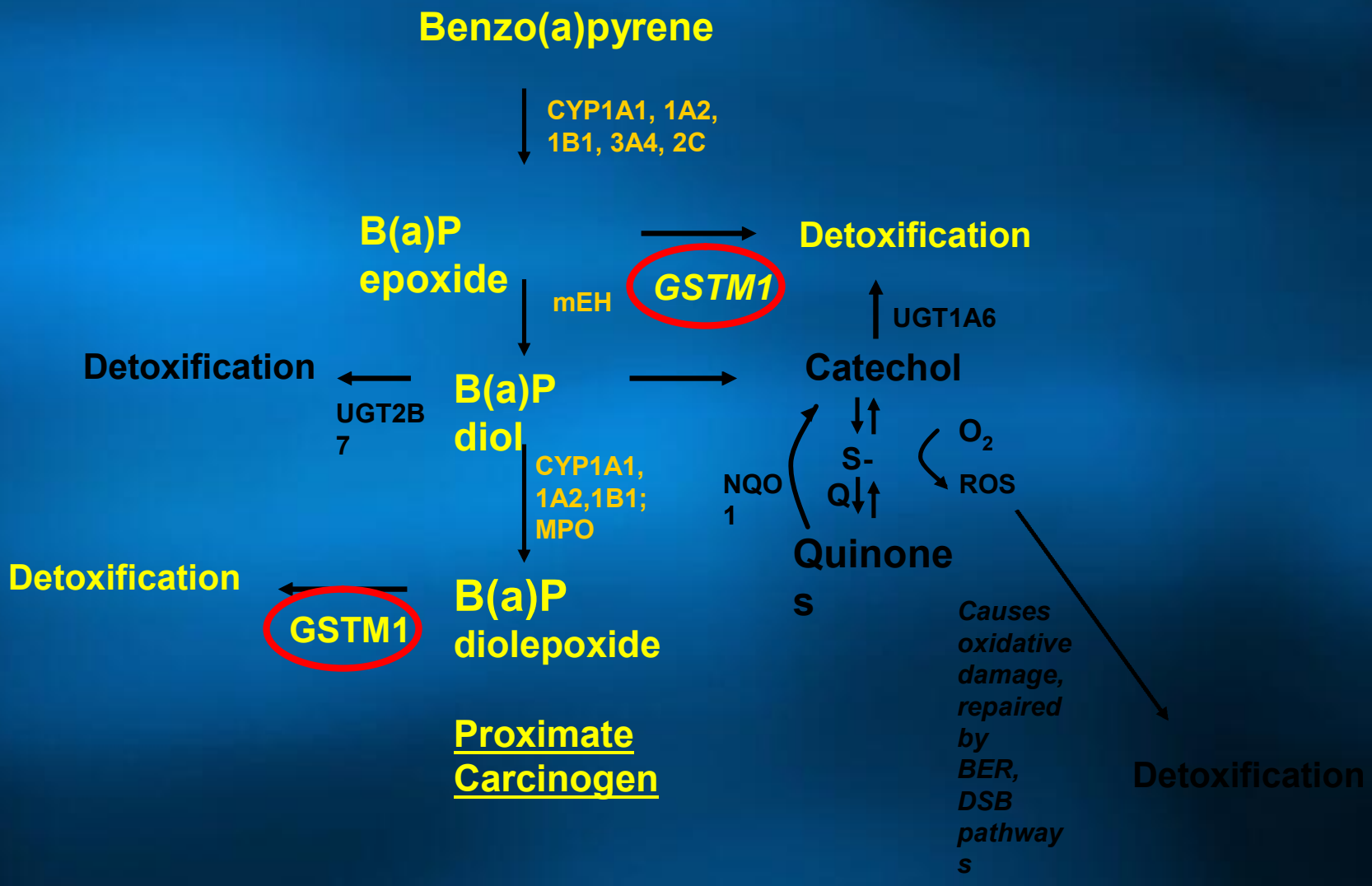
  OR = 0.3, 95% CI: 0.1-1.0, p = 0.05

- **General population (6360 cases, 41 studies):**

  OR =1.35, 95%CI: 1.21-1.50, p = 10^{-6}

(Garcia-Closas et al., Lancet 2005; Carreon et al., IJC, 2006; Rothman et al., IJE, 2007, Garcia-Closas in prep)

Role of GSTM1 in in Benzo(a)pyrene Detoxification



GSTM1 null Genotype and Bladder Cancer Risk,

- **Overall (6,700 cases, 35 studies)**

  OR = 1.44, 95% CI: 1.30-1.60, p = 10^{-12}

- **Case-only interaction OR of effect in smokers / nonsmokers (4,000 cases, 17 studies)**

  OR= 1.0, 95% CI: 0.9-1.2, p = 0.86

Garcia-Closas et al., in prep: Garcia-Closas et al., Lancet 2005

Conclusions

- Effects of genetic polymorphisms may be highly exposure specific

- High quality exposure data should be collected in well-designed studies, and taken into account early in the analysis of candidate gene or genome-wide scans